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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.

By: Evelyn Gomez

Appl. No.	:	09/250,056	Confirmation No. 1647
Applicant	:	James D. Marks, et al.	
Filed	:	February 12, 1999	
TC/A.U.	:	1642	
Examiner	:	Larry R. Helms	
Docket No.	:	407J-895030US	
Customer No.	:	22798	
Client Ref No.:		98-232-4	

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Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132
[M.P.E.P. § 715.01(c)]

I. I, James D. Marks, MD, Ph.D., am a Professor in Residence at the University of California, San Francisco, in the Department of Anesthesia and Pharmaceutical Chemistry and a Program Member of the UCSF Comprehensive Cancer Center. Accompanying this Declaration is a copy of my Biographical Sketch. As should be apparent from this information, I am an expert in the field of immunology, particularly as it relates to cancer/tumor-related antigens and antibodies. I am an inventor of the above-identified application.

II. The epitopes bound by the antibodies designated as F5 and C1 in US Patent Application No. 09/250,056 are not the same epitopes that are bound by the TA1 antibody reported by Xu et al. (Int. J. Cancer 53:401-408, 1993) and Maier et al. (Cancer Res. 51:5361-5369, 1991).

III. The proto-oncogene c-ErbB-2 (also termed *HER2*) encodes a 185 kD tyrosine kinase receptor of the EGF receptor family. While the nature or function of the natural ligand of c-ErbB-2 remain uncertain, it is known that the molecules of c-ErbB-2, as part of their receptor activity, a) associate with each other as well as with the other members of EGFR family, b) undergo phosphorylation of their intracellular domains, c) evoke a cascade of intracellular processes leading, e.g., to the modulation of cell growth, and d) undergo internalization into the cell. A number of murine monoclonal antibodies in the art have been shown to bind to the ErbB2 receptor and induce the above-described cellular responses to various degrees. It was noted, for example, by Maier, et al. (1991) that antibodies that cause a cellular response of similar nature and magnitude are likely to bind to the same epitope. Accordingly, antibody binding to different epitopes within the receptor structure often leads to differing cellular responses to such binding (i.e., dissimilar rates of internalization, or effectiveness as a growth inhibitor). Furthermore, binding of different antibodies to the same epitope can be demonstrated using a competition assay.

IV. F5 and C1 antibodies recognize the same epitope. Binding of the F5 and/or C1 epitope of the c-ErbB-2 receptor by the antibody sequences of the claimed invention leads to extremely rapid internalization of the antibody into ErbB2-expressing cancer cells, such as SKBr-3 cells (Example 2, starting at page 61). Cellular binding of phage expressing F5, C1 or C6.5 sequences was inhibited in a competition assay by increasing concentrations of soluble scFv-F5, scFv-C1 or scFv-C6.5 (see, for example, Figure 2 in the specification). One of skill in the art would surmise that F5 and C1 recognize similar epitopes, based upon the demonstrated cross-reactivity in the competition studies as well as similarities in dissociation constants and internalization rates (page 69, lines 14-28 of the specification).

V. A "sandwich ELISA" study can be used to compare the availability of epitopes on the surface of an antigen to interaction with antibodies. If an antigen presents two different epitopes that can be bound by two different antibodies (one of which may be associated with a cell surface), the antigen will be "sandwiched" between

them. If the same epitope (or two closely spaced epitopes) are involved, then only one of the antibodies is able to associate with the antigen and no "sandwich" is formed.

VI. TA1 recognizes a different epitope on the c-erbB2 receptor than F5. A sandwich binding assay similar to an ELISA study was performed to compare the availability of the epitopes on c-erbB2 receptor. Yeast strain EBY100 was transformed to express one of the three single chain anti-c-erbB2 antibodies on the cell surface: F5 (Y-F5 cells); ML3.9, a mutant version of the IgG antibody C6.5 (Y-ML3.9 cells), or 4D5 (Y-4D5 cells). The antibody constructs expressed on the yeast surface were allowed to bind to the extracellular domain of the c-erbB2 receptor (recombinant ErbB2 ECD). A humanized form of 4D5 (Herceptin®), TA-1 and C6.5 were then added to the cells, followed by labeling with a fluorescent dye (anti-human (Fc specific) Fab'2 phycoerythrin conjugate), and the cells were examined by flow cytometry.

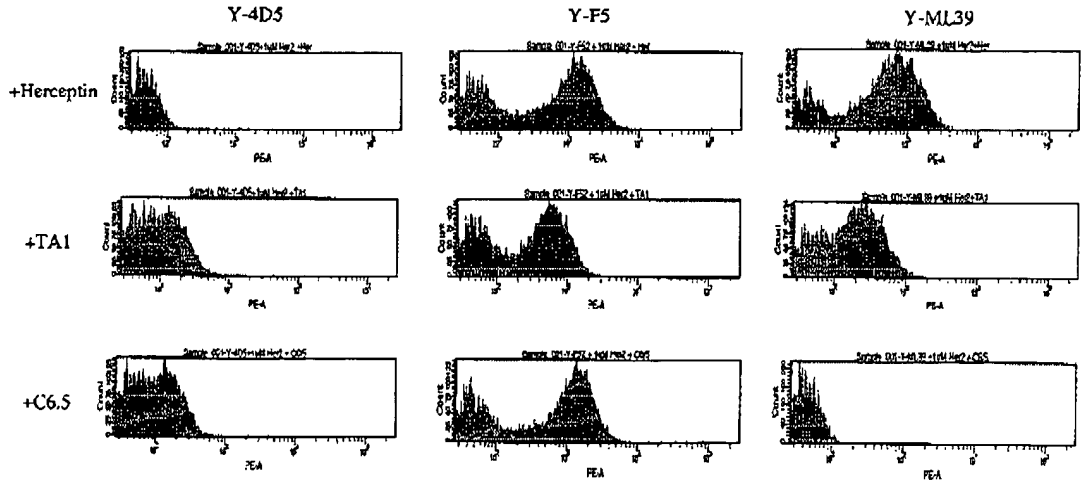


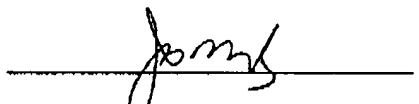
Figure 1. Flow cytometric analysis of antibody binding to ErbB2 ECD after capture by yeast displayed single chain Fv antibodies 4D5 (Y-4D5), F5 (Y-F5), and ML3-9 (Y-ML3-9).

As can be seen in the middle column of Figure 1, the recombinant ErbB2 ECD associated with the yeast cells expressing F5 was able to interact with Herceptin,

(top), TA-1 (middle), and C6.5 (bottom), indicating that the epitope bound by F5 differs from that recognized by these three antibodies. In contrast, Herceptin is unable to bind to recombinant ErbB2 ECD captured by Y-4D5 cells (top left panel in Figure 1), and C6.5 IgG does not bind to recombinant ErbB2 ECD captured by Y-ML3.9 cells (bottom right panel in Figure 1). This is as expected, since the antibody expressed on the yeast surface and the second antibody bind the same epitope. The data clearly show that the F5 does not bind to the same epitope as the TA-1 antibody.

VII. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



James D. Marks, MD, Ph.D.

4/5/05

Date

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
James D. Marks, M.D., Ph.D.	Professor of Anesthesia and Pharmaceutical Chemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Berkeley			Biochemistry
University of California, San Francisco	M.D.	1979	Medicine
Medical Research Council, Laboratory of Molecular Biology, Cambridge, England	Ph.D.	1992	Molecular Biology

A. Positions and Honors

1979-1982	Residency in Internal Medicine, University of California, San Francisco		
1982-1983	Fellowship in Critical Care Medicine, University of California, San Francisco		
1983-1984	Assistant Professor of Medicine, University of California, San Francisco		
1984-1986	Residency in Anesthesia, University of California, San Francisco		
1986-1989	Assistant Professor of Anesthesia and Medicine, University of California, San Francisco		
1992-1994	Assistant Professor of Anesthesia and Pharmaceutical Chemistry;		
1994-1998	Associate Professor of Anesthesia and Pharmaceutical Chemistry		
1997-2001	Director, Medical-Surgical Intensive Care Unit, San Francisco General Hospital		
1998-present	Professor of Anesthesia and Pharmaceutical Chemistry		
1975	Phi Beta Kappa	1979	Alpha Omega Alpha
1994	Beckman Young Investigator Award	1995, 96	CaPCURE Research Award
1983	Board Certification, American Board of Internal Medicine		
1988	Board Certification, American Board of Anesthesiology		
1993	Board Certification, Critical Care Medicine via American Board of Anesthesiology		

B. Selected peer-reviewed publications (30 of 123)

1. Marks JD, Hoogenboom HR, Bonnert TP, McCafferty J, Griffiths AD, Winter G. Bypassing immunization: Human antibodies from V-gene libraries displayed on phage. J. Mol. Biol. 222: 581-597, 1991.
2. Marks JD, Griffiths AD, Malmqvist, M., Clackson T, Bye JM and Winter G. Bypassing immunization: High affinity human antibodies by chain shuffling. Bio/Technology. 10: 779-783, 1992.
3. Marks JD, Hoogenboom HR, Griffiths AD and Winter G. Molecular evolution of proteins on filamentous phage: mimicking the strategy of the immune system. J. Biol. Chem. 267: 16007-16010, 1992.
4. Griffiths, AD, Malmqvist, M, Marks, JD, Bye, JM, Embleton, MJ, McCafferty, J, Baier, M, Holliger, KP, Gorick, BD, Hughes-Jones, NC, Hoogenboom, HR and Winter, G. Human anti-self antibodies with high specificity from phage display libraries. EMBO. J. 12: 725-734, 1993.
5. Marks JD, Ouwehand WH, Bye JM, Finnern R, Gorick BD, Voak D, Thorpe S, Hughes-Jones NC, Winter G. Human antibody fragments specific for human blood group antigens from a phage display library. Bio/Technology. 10: 779-783, 1993.
6. Figini M, Marks JD, Winter G, Griffiths AD. Diversifying antibody binding sites: template directed selection using repertoires of Fab fragments assembled on phage *in-vitro*. J. Mol. Biol. 239: 68-78, 1994.
7. Schier R, Bye J, McCall A, Adams GP, Weiner LM, Marks JD. Isolation of high affinity human anti-c-erbB-2 single chain Fv using affinity driven selection. J. Mol. Biol. 255: 28-43, 1996.
8. Schier R, Balint RF, McCall A, Apell G, Larrick JW, Marks JD. Identification of functional and structural amino acid residues by parsimonious mutagenesis. Gene. 169: 147-155, 1996.
9. Schier R, McCall A, Adams GP, Marshall K, Yim M, Merritt H, Crawford RS, Weiner LM, Marks JD. Isolation of high affinity anti-c-erbB2 single-chain Fv by molecular evolution of the complementarity determining regions in the centre of the antibody combining site. J. Mol. Biol. 263: 551-567, 1996.

10. Marks C and Marks JD. Phage libraries: a new route to clinically useful antibodies. N. Engl. J. Med. 335: 730-734, 1996.
11. Adams GP, Schier R, Marshall K, Wolf EJ, McCall A, Marks JD and Weiner LM. Influence of affinity on the in vitro and in vivo binding properties of human single chain Fv molecules directed against c-erbB-2. Cancer Res. 58: 485-490, 1998.
12. Adams, GP, Schier R, Marshall K, Wolf EJ, McCall A, Weiner LM and Marks JD. Prolonged in vivo tumor retention of a human diabody targeting the extracellular domain of human HER2/neu. Brit. J. Cancer. 77: 1405-1412, 1998.
13. Sheets MD, Amersdorfer P, Finnern R, Sargent P, Lindqvist E, Schier R, Hemingsen G, Wong C, Gerhart JC, Marks JD. Efficient construction of a large non-immune phage antibody library: The production of panels of high affinity human single chain antibodies to protein antigens. Proc. Natl. Acad. Sci. USA. 95: 6157-6162, 1998.
14. McCall AM, Amoroso AR, Sautes C, Marks JD and Weiner LM. Characterization of anti-mouse Fc gamma RII single-chain Fv fragments derived from human phage display libraries. Immunotechnology. 4: 71-87, 1998.
15. Becerril B, Poul M-A and Marks JD. Towards selection of internalizing antibodies from phage libraries. Biochem. Biophys. Res. Comm. 255, 386-393, 1999.
16. Poul M-A and Marks JD. Targeted gene delivery to mammalian cells by filamentous bacteriophage. J. Mol. Biol. 288: 203-211, 1999.
17. Poul, M-A, Becerril B, Nielsen UB, Morisson P, and Marks JD. Selection of tumor specific internalizing human antibodies from phage libraries. J. Mol. Biol. 301: 1149-1161, 2000.
18. Liu B, Marks JD. Applying phage antibodies to proteomics: selecting single chain Fv antibodies to antigens blotted on nitrocellulose. Anal Biochem. 286:119-128, 2000.
19. Nielsen UB, Adams GP, Weiner LM, Marks JD. Targeting of bivalent anti-ErbB2 diabody antibody fragments to tumor cells is independent of the intrinsic antibody affinity. Cancer Res. 60:6434-40, 2000
20. Neve RM, Nielsen UB, Kirpotin DB, Poul MA, Marks JD, Benz CC. Biological Effects of Anti-ErbB2 Single Chain Antibodies Selected for Internalizing Function. Biochem Biophys Res Commun. 280(1):274-279, 2001.
21. Heitner T, Moor A, Hasan T, Garrison J, Marks C, and Marks JD. Selection of cell binding and internalizing epidermal growth factor receptor antibodies from a phage display library. J. Immunol. Meth. 248: 17-30, 2001
22. Huie MA, Cheung, M-C, Muench MO, Becerril B, Kan YW, and Marks JD Antibodies to human fetal erythroid cells from a nonimmune phage antibody library Proc. Natl. Acad. Sci. 98: 2682-2687, 2001.
23. Park JW, Hong K, Kirpotin DB, Colbern G, Shalaby R, Baselga J, Shao Y, Nielsen UB, Marks JD, Moore D, Papahadjopoulos D, and Benz CC. Anti-HER2 immunoliposomes: enhanced anticancer efficacy due to targeted delivery. Clin. Cancer Res. 8:1172-1181, 2002.
24. Nielsen UB, Kirpotin DB, Pickering EM, Hong K, Park JW, Shalaby MR, Shao Y, Benz CC, and Marks JD. Therapeutic efficacy of anti-ErbB2 immunoliposomes targeted by a phage antibody selected for cellular endocytosis. Biochim. Biophys. Acta 159:109-118, 2002.
25. O'Connell D, Becerril B, Roy-Burman A, Daws M, and Marks JD. Phage vs phagemid libraries for generation of human monoclonal antibodies. J. Mol. Biol. 321:49-56, 2002.
26. Mamot C, Drummond DC, Greiser U, Hong K, Kirpotin DB, Marks JD, Park JW. EGFR-targeted immunoliposomes mediate specific and efficient drug delivery to EGFR- and EGFRvIII-overexpressing tumor cells. Cancer Res. 63:3154-3161, 2003.
27. Liu B, Conrad F, Cooperberg MR, Kirpotin D, Marks JD. Mapping tumor epitope space by direct selection of antibody gene diversity library on prostate cancer cell surfaces. Cancer Res. 64:704-710, 2004.
28. Weaver-Feldhaus JM, Lou J, Coleman JR, Siegel RW, Marks JD, and Feldhaus M. Yeast mating for combinatorial Fab library generation and surface display. FEBS Letters. 23:24-34, 2004.
29. Adams GP, Shaller CC, Dadachova K, Simmons HH, Horak EM, Tesfaye A, Marks JD, Brechbiel MW, Weiner LM. A Single Treatment of ^{90}Y-CHX-A" C6.5 Diabody Inhibits the Growth of Established Human Tumor Xenografts in Mice. Cancer Res. 64:6200-6206, 2004.
30. Robinson MK, Doss M, Shaller C, Narayanan D, Adler LP, Gonzalez Trotter DE, Marks JD, and Adams GP. Quantitative immunoPET imaging of HER2-positive xenografts with an Iodine-124 labeled anti-HER2 diabody. Cancer Res. 65:1471-1478, 2005.

C. **Research Support**

Ongoing Research Support

NIH R21 AI53389-01 Marks (PI) 09/01/02-08/31/2005
NIAID/NIH
Deciphering toxin neutralization by oligoclonal antibody
The major goals of this project are to identify the mechanism by which combining monoclonal antibodies synergize to neutralize botulinum neurotoxin
Role: PI

P50 CA58207 Gray (PI) 04/01/97-11/20/07
NCI/NIH
Phage display antibodies
The major goals of this project are to isolate and engineer recombinant human anti-ERBB2 antibodies for immunoliposome therapy of breast cancer.
Role: Project Leader

Prostate Cancer SPORE Shuman (PI) 12/01/00-11/30/05
NCI/NIH
Antibody gene diversity libraries and phage display to generate human antibodies for prostate cancer therapy
The goals of this project are to: 1) generate new phage antibody libraries; 2) select antibodies which bind specifically to prostate cancer cells; and 3) use the antibodies to isolate novel prostate cancer surface antigens.
Role: Project Director

U54 IRT/MTA, Mechanism-Based Evaluations of ErbB-Targeted Therapeutics Tempero (PI) 09/01/01-09/30/05
NCI/NIH
Novel phage antibody-based probes of ErbB receptor function
The aims of this proposal are to generate probes for the functional assessment of the ErbB family of RTKs, including EGF (ErbB1), ErbB2, ErbB3 and ErbB4 receptors. The probes will be used for mechanism-based evaluation of novel ErbB targeted strategies
Role: Project Director

P50 CA97257 Park (PI) 08/31/02-04/30/07
NCI/NIH
Novel Targeted Drug Delivery for Brain Tumor Treatment
The major goals are to construct immunoliposomes to brain tumor cells; optimize immunoliposomes in conjunction with regional delivery methods in preclinical glioma models; evaluate anti-EGFR immunoliposomes for targeted delivery of anticancer agents; construct new brain tumor-targeted immunoliposomes; perform advanced preclinical studies and clinical development of best construct.
Role: Coinvestigator

UO1 AI056493 Marks (PI) 06/01/03-05/31/08
NIH/NIAID
Development of Botulinum Neurotoxin Immunotherapy
The overall goal is to generate neutralizing human compatible monoclonal antibodies (mAbs) to the BoNTs for prevention and treatment of botulism resulting from intentional exposure to toxin.
Role: PI

Completed Research Support

DAMD17-97-7250 (Marks) 09/01/97-08/31/00
Department of Defense
Structural basis of EGFR Dimerization for Drug Design
The major goal was to evaluate the role of the epidermal growth factor receptor (EGFR) in breast cancer by expressing and purifying EGFR and solving the atomic structure.
Role: PI

DAMD17-96-1-6244 (Marks) 09/01/96-03/31/99
Department of Defense
Specific targeting of retroviral vectors for breast cancer therapy
Role: PI

DAMD17-94-J-4433 (Marks) 08/15/94-08/14/99
Department of Defense
Selection of Human Antibody Fragments which Bind Novel Breast Tumor Antigens
The major goal was to isolate human scFv antibody fragments which bind breast tumor antigens by selecting a pre-existing nonimmune scFv phage antibody library on primary and metastatic breast tumor cell lines with and without prior depletion of the library on normal cells.
Role: PI

DAMD17-98-C-8030 Marks (PI) 05/01/98-02/28/03
U.S. Army Medical Research Institute of Infectious Disease
Human monoclonal antibodies which neutralize botulinum neurotoxin
The major goals of this project are to produce human monoclonal antibodies, which neutralize botulinum neurotoxin serotypes A, B, and E.
Role: PI

DAMD17-98-1-8189 Marks (PI) 07/01/98-08/30/02
U.S. Army Medical Research and Materiel Command
Identification of novel breast cancer antigens using phage antibody libraries
The major goals of this project are to use immune and non-immune phage antibody libraries to identify novel breast tumor antigens for use as therapeutic targets.
Role: PI

DOD BC970094 Weiner (PI) 09/01/98-08/31/02
U.S. Army Medical Research and Materiel Command
Targeting breast cancer with anti-her2/neu diabodies
The major goals of this project are to engineer the anti-ErbB2 C6.5 diabody for preclinical and clinical radioimmunotherapy trials
Role: Subcontract Co-investigator

R01 CA65559 Weiner (PI) 07/01/00-05/31/03
NCI/NIH
Tumor Targeting by Single-chain Fv Molecules
The major goals of this project are to create a pre-targeted radioimmunotherapy strategy employing bispecific antibodies targeting HER2/neu and haptens to localize radiometals to tumor sites and to demonstrate that pretargeted radioimmunotherapy is superior to conventional radioimmunotherapy.
Role: Subcontractor Co-investigator